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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,662	VANDEKERCKHOVE ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/11/05, 2/22/08* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment filed 7/13/2009 is acknowledged and has been entered. Claims 1, 5, and 13 were amended. Accordingly, claims 1-7 and 13-14 are currently pending and subject to examination below.

Objections/ Rejections Withdrawn

2. Applicant's amendments have overcome the objection to claim 1 and the rejections of claims 1-7 and 13-14 under § 112, 1st and 2nd paragraphs as set forth in the previous Office action.

Priority

3. Acknowledgment is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/EP03/50402, filed 9/11/2003.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Creighton, T.E. ("Proteins: Structures and Molecular Properties" Second Edition, W.H. Freeman and Company, New York, 1993), pages 10-20 and 31-41) in view of Aebersold et al. (U.S. 6,670,194 B1).

Creighton teaches diagonal techniques for the purification of peptides (i.e., specific interaction partners), in which those peptides in a peptide mixture that contain a particular amino acid are selectively isolated in two electrophoretic or chromatographic steps, which are performed with an intervening step modification step that alters the mobilities of modified peptides (see page 41). Specifically, the reference teaches (a) adding a compound (e.g., iodoacetic acid, cyclohexanedione, or trifluoroacetyl, maleyl, or dinitrophenyl groups) to a complex mixture of peptides, wherein the compounds covalently modify specific amino acid residues in a peptide to form modified amino acid residues (see page 41 and also at pages 10-20 and 38-40, in particular at Equations 1.84, 1.22, 1.45, 1.79, 1.80, and 1.29).

Creighton further teaches (b) performing a first separation step, which may be performed either by electrophoresis or by the more common high-pressure liquid chromatography (HPLC) analysis (page 41, right column, the second full paragraph; and left column, the first full paragraph).

After the first separation, fractions are (c) subjected to an intervening modification so as to change the properties of the peptides which have been selectively modified by the compound. For example, the compound maleic anhydride can be added to modify lysine-containing peptides (page 41, right column and page 11, left column including Equation 1.22). After the first separation, the compound is removed (i.e., altered). As another example, the compound cyclohexanedione can be added to selectively modify arginine-containing peptides (page 41, right column and page 12, right column including Equation 1.29). After the first separation, arginine residues are regenerated by alkaline pH treatment (i.e., the cyclohexanedione compound is removed).

When the peptides are (d) subjected to the same separation procedure a second time, peptides that have been modified by the compound will be isolated (see left column, the second full paragraph). As explained on page 41, third paragraph, when using HPLC chromatography, fractions must be modified and then reanalyzed (i.e., re-chromatographed). Similar techniques can also be performed for chemical modification of a variety of amino acids using different compounds (page 41, right column; and pages 10-10).

The compounds taught by Creighton possess the functional limitations claimed because they are capable of reacting with a functionality present in the interacting peptides. For example, cyclohexanedione as taught by Creighton is capable of reacting with the arginine-containing peptides as discussed above. Because these two moieties react in a specific manner, the chemical structure of cyclohexanedione may also be said to determine the specific interaction thereof. In addition, the compounds are altered after the first separation as discussed above. With respect to the recitation that complexes containing the altered compound elutes at a different elution time as

compared to complexes containing non-altered compound, Creighton makes clear that the mobilities of peptides that have been modified after the first separation are different in the second separation. Because the peptides have different mobilities, this is strong scientific evidence that the peptides would in fact elute at different elution times.

The teachings of Creighton differ from the instantly claimed invention in that the reference fails to specifically teach that the compounds used in the diagonal techniques do not interact with the majority of molecules in the complex mixtures. The reference makes clear that the compounds selectively interact with peptides containing particular amino acids, but is silent regarding the proportion of peptides in the mixtures would interact with the compound.

However, those of skill in the art at the time of the instant invention recognized the value in performing large-scale analyses of proteins in a so-called "proteomics" approach.

Aebersold et al. discuss the recognized importance of proteins in biological processes. Like large-scale genomic analysis, global analysis of proteins expressed in a cell or tissue is also essential to describe a biological system (column 1, lines 20-60). Such complex samples can be analyzed in order to identify proteins in the context of disease states (column 3, lines 8-46). Techniques to assay proteins expressed in complex samples (such as blood, cells, tissues, and fractions thereof) are therefore desirable (see column 1, line 60 to column 3, line 45). It is noted that the instant specification indicates that the proteome is a complex mixture of proteins that in most cases has 100 different proteins or more (page 23, lines 26-35). Further, it is disclosed that a proteome is present in such samples as intact cells, lysate, biological fluid, etc. (ibid). Because

these same samples are taught by Aebersold et al., it is presumed that they would necessarily contain 100 different proteins or more.

In addition, Aebersold et al. also teach simultaneous "multiplex" analysis of multiple proteins or of multiple samples in a single analysis (see column 6, lines 40-45; column 7, lines 37-42). For example, sequence identification of multiple peptide components of a protein mixture can be obtained in a single analysis (see also heading to Table 2).

To accomplish this goal of assaying proteins in complex samples, Aebersold et al. set forth a basic approach to analyze and detect specific proteins in complex samples (see especially at column 2, lines 49-57). Their approach involves selectively labeling and isolating specific peptide fragments from complex mixtures, and then characterizing the isolated peptides by mass spectrometric techniques (column 3, line 39 to column 7, line 42).

Similar to the labeling of specific amino acids such as cysteine as taught by Creighton, the labeling methods of Aebersold et al. also involve the use of compounds that have specific reactivity for certain protein groups, such as for sulfhydryl groups on cysteines (see Aebersold et al. for example at column 4, lines 27-39; column 6, lines 49-59; column 10, lines 30-43; column 15, line 54 to column 16, line 24). Next, proteins in the labeled sample are cleaved into peptides, and the labeled peptides are selectively isolated using chromatography procedures (see Aebersold et al. at column 5, lines 44-51; column 7, lines 10-15). Finally, labeled peptides are characterized by mass spectrometric techniques, e.g. to determine their amino acid sequence and identify the originating protein (column 3, line 39 to column 7, line 42 and especially at column 4, lines 54-60; see also at column 12, line 62 to column 13, line 65; and at columns 36-38).

The methods of Aebersold et al. are therefore highly analogous to those of Creighton in that they involve selectively labeling certain protein groups (e.g., cysteines) and then isolating peptides that have been labeled.

Therefore, it would have been obvious to one of ordinary skill in the art to perform the diagonal chromatography techniques of Creighton on complex samples such as blood, cells, tissues, and fractions thereof (as taught by Aebersold et al.).

One would be motivated to apply the diagonal chromatographic techniques to the analysis of complex mixtures (such as blood or cells) in order to conduct large-scale proteomic analysis, in view of the teachings of Aebersold et al. that the large-scale analysis of proteins (proteomics) is essential in order to completely describe a biological system. More generally, one would be motivated to analyze very complex samples such as blood, cells, or tissue as taught by Aebersold et al. because Aebersold et al. taught that analysis of proteomes can be used to identify proteins whose expression level is changed in response to various disease states. Therefore, one would be motivated to study complex biological samples in order to identify proteins that play a role in disease. More generally, when taken together with the teachings of Aebersold et al. that the large-scale analysis of proteins expressed in a cell or tissue is important for completely describing a biological system, one would have been motivated to analyze samples containing as many proteins as possible in order to obtain as much information as possible about a particular biological system.

When employing the diagonal techniques of Creighton et al. to analyze complex mixtures such as blood, it would seem that the compounds of Creighton et al. would necessarily interact only with a minority of the molecules present in such complex samples. In particular, in view of

the general knowledge in the art that blood contains not only proteins but also lipids, cells, vitamins, small molecules, ions, etc., there is a strong scientific basis to suggest that the compounds, being selective for specific amino acids, would necessarily interact only with a minority of the total molecules present in blood samples. For example, when employing iodoacetic acid, cyclohexanedione, or trifluoroacetyl, maleyl, or dinitrophenyl groups as taught by Creighton et al. in order to modify peptides in complex samples such as blood (as taught by Aebersold et al.), it is presumed absent evidence to the contrary that these compounds would covalently modify a minority of the molecules in blood.

For these reasons, when employing the diagonal chromatography methods of Creighton to analyze complex samples such as blood, the recited feature would necessarily follow.

One would have a reasonable expectation of success in employing the diagonal chromatography procedures of Creighton to analyze complex samples because the teachings of Aebersold et al. indicate that proteins which have been selectively labeled and isolated from complex mixtures can be successfully analyzed according to known methods, namely by mass spectrometry. Consequently, one of ordinary skill in the art would expect success in applying the methods of Creighton to analyze complex samples such as blood in conjunction with mass spectrometry analysis of the isolated, labeled peptides.

In addition, because Aebersold et al. also teach that their methods are compatible with any fractionation methods that reduce the complexity of the sample (column 16, lines 20-24), one of ordinary skill in the art would have had a reasonable expectation of success in analyzing complex mixtures fractionated by the methods of Creighton by the mass spectrometry techniques of Aebersold et al.

With respect to claim 2, Creighton teaches a "mixture of peptides" as discussed above. Aebersold et al. teaches samples such as blood, cells or tissue (i.e., complex mixtures of proteins).

With respect to claims 3-4, it is acknowledged that Creighton fails to specifically teach adding the compound to a complex protein mixture that is then *cleaved* into a protein peptide mixture prior to separation step (b). Rather, in Creighton the compound is added to a protein peptide mixture; there is no specific teaching of a step in which the peptides are initially obtained by cleavage of proteins.

However, Aebersold et al. also teaches digesting labeled protein samples with proteases to produce peptide fragments prior to analysis by mass spectrometry (column 3, lines 39-68; column 5, lines 33-60; column 12, lines 44-53). In particular, Aebersold et al. exemplify adding a labeling reagent to a complex protein mixture, which is then cleaved into peptide fragments; peptide fragments that are labeled are then isolated and identified (ibid). By isolating and analyzing the isolated peptide fragments, the presence of protein(s) in the sample can be determined since the peptides are characteristic of the originating protein (column 3, lines 39-68). For example, sequence identification of multiple peptide components of a protein mixture can be obtained in a single analysis (see also heading to Table 2). Since the resulting peptide fragments are characteristic of the presence of the protein from which they originated, isolation and characterization of the peptide fragments can be used to determine the presence of the protein in the complex mixture (see also the abstract).

As discussed above, the affinity labeling reagent of Aebersold et al. (which may react with sulfhydryl groups) is highly analogous to the iodoacetic acid modifying reagents of Creighton et al., which may also be sulfhydryl reactive.

Therefore, when performing the method of Creighton in order to analyze complex samples such as blood, cells or tissue (as taught by Aebersold et al.), it would have been obvious to treat the samples with a protease as taught by Aebersold et al. (thereby cleaving proteins therein to form a protein peptide mixture) as a necessary step prior to analysis by mass spectrometry. In particular, one would be motivated to digest the sample into peptide fragments so that the presence of the protein from which the fragments originated could be identified. Although Creighton exemplifies labeling a mixture of peptides, it would have been obvious to first label the complex mixtures of proteins (e.g., blood, cells, tissue) taught by Aebersold with the labeling compound of Creighton and to subsequently digest the sample into a protein-peptide mixture because this order is exemplified in the analogous methods of Aebersold et al. In addition, the selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results. See MPEP 2144.04.

Motivation to combine the reference teachings in this manner also comes from the teachings of Creighton, since the diagonal chromatography procedures are performed on mixtures of peptides.

With respect to claims 5-7, Aebersold et al. teach that isolated peptides can be characterized by mass spectrometric techniques: in particular, the sequence of isolated peptides can be determined using mass spectrometry techniques, and by application of sequence database searching techniques, the protein from which the sequenced peptide can be identified using the

mass spectrometry data (which measures the peptide masses). See column 3, lines 54-60; and columns 13-14.

Therefore, when performing the peptide isolation method of Creighton on a complex protein mixture in order to identify proteins in the mixture (as taught by Aebersold et al.), it would have been further obvious to one of ordinary skill in the art at the time of the instant invention to identify the isolated peptides by mass spectrometry in combination with sequence database searching as taught by Aebersold et al. because Aebersold et al. taught that isolated peptides can be sequenced and characterized by mass spectrometry in this manner, thereby allowing identification of the protein from which they originate, and consequently allowing for determination of the presence of that protein in the complex mixture.

7. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Creighton in view of Aebersold et al. as applied to claim 1 above, and further in view of the evidence of Sahasrabudhe (U.S. 5,705,351) or Chang (U.S. 5,474,780).

Creighton is as discussed above, which teaches compounds including fluoro-2,4,-dinitrobenzene and maleic anhydride to modify specific amino acid residues (see especially page 41, right column; page 31, right column; and page 11, left column). However, the reference is silent as to whether such compounds are drugs.

Sahasrabudhe provides evidence that fluoro-2,4-dinitrobenzene is a drug[1] in that it can be used to chemically treat cells for therapy of non-leukemic cancer (column 3, line 34 to column 4,

[1] A "drug" is defined in the art as "a substance intended for use in the diagnosis, cure, treatment, or prevention of disease"; "a substance that has a particular effect on the body" (Penguin English

line 16; column 17, lines 29-49). In addition, fluoro-2,4-dinitrobenzene can be used in diagnosis, e.g. to identify patients at risk of cancer or to monitor therapy in cancer patients (column 7, line 31 to column 8, line 2; column 14, line 31 to column 15, line 28).

Chang teaches that maleic anhydride is used as an ingredient in medical preparations for drug delivery (abstract and column 3, lines 1-21).

Therefore, in light of the evidence of Sahasrabudhe and Chang, the teachings of Creighton and Aebersold et al. meet the claim as the compounds taught by Creighton are drugs.

8. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Creighton in view of Aebersold et al. as applied to claim 1 above, and further in view of GE Healthcare ("Fraction Collectors: Frac-950 and Frac-920", Data File 18-1153-57 AD (May 2001), retrieved from http://www1.gelifesciences.com on 4/8/09).

Creighton and Aebersold et al. are as discussed above. Creighton teaches HPLC chromatography but fails to provide details regarding the specific procedures to be used. Therefore, the references fail to specifically teach pooling fractions to avoid elution overlap between different peaks.

However, it was known in the art to adjust the size of collected fractions when performing chromatographic procedures in order to avoid re-mixing of proteins separated on the column. See GE Healthcare at column 3, "Collect the fractions you want", where it is discussed

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Dictionary); "any substance used as an ingredient in medical preparations"; "any substance that affects the normal body functions" (Collins Dictionary of Biology).

that while too many fractions will make for too much work (many tubes), while a fraction size that is too large will result in loss of resolution as peaks separated on the column will be re-mixed in the collected fractions. GE Healthcare teaches that by using automated peak fractionation, peak overlap can be reduced (Figure 7).

Therefore, it would have been obvious to one of ordinary skill in the art to employ automated peak fractionation, thereby pooling fractions having distinct elution times in such a way as to reduce peak overlap, because GE Healthcare taught that such procedures achieve the best results in chromatography (which is the technique employed by Creighton).

Response to Arguments

9. Applicant's arguments filed 7/13/2009 have been fully considered.

10. With respect to the rejections of claims 1-7 under § 103 as being unpatentable over Creighton in view of Aebersold, Applicant's arguments have been fully considered but are not found persuasive.

11. Applicant argues that the references fail to specifically teach that the compound does not interact with the majority of molecules in the mixture (Reply, pages 6-8).

This is not found persuasive because as discussed above, Creighton et al. teaches compounds that selectively interact with particular amino acids. Aebersold et al. suggests that such compounds may be used for proteomic analyses conducted on complex samples such as blood or tissue. Since such complex samples contain numerous types of molecules (including not only protein but also lipids, vitamins, ions, cells, etc.), there is a strong scientific basis to believe

that the compounds of Creighton et al. would not interact with the majority of molecules found in blood, for example. Consequently, it is presumed absent evidence to the contrary that when employing the diagonal techniques of Creighton to analyze the complex samples of Aebersold et al., it would necessarily follow that the amino acid-selective compounds with not interact with the majority of molecules in the sample.

12. Applicant does not separately argue the limitations of dependent claims 13-14 (see Reply, page 9).

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by

telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Mark L. Shibuya/
Supervisory Patent Examiner, Art Unit 1641